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Mediators of the Impact of Hourly Net Ultrafiltration Rate on Mortality in Critically Ill Patients Receiving Continuous Renal Replacement Therapy

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Objectives: During continuous renal replacement therapy, a high net ultrafiltration rate has been associated with increased mortality. However, it is unknown what might mediate its putative effect on mortality. In this study, we investigated whether the relationship between early (first 48 hr) net ultrafiltration and mortality is mediated by fluid balance, hemodynamic instability, or low potassium or phosphate blood levels using mediation analysis and the primary outcome was hospital mortality.

Design: Retrospective, observational study.

Setting: Mixed medical and surgical ICUs at Austin hospital, Melbourne, Australia.

Patients: Critically ill patients treated with continuous renal replacement therapy within 14 days of ICU admission who survived greater than 48 hours.

Interventions: None.

Measurements and Main Results: We studied 347 patients (median [interquartile range] age: 64 yr [53–71 yr] and Acute Physiology and Chronic Health Evaluation III score: 73 [54–90]). After adjustment for confounders, compared with a net ultrafiltration less than 1.01 mL/kg/hr, a net ultrafiltration rate greater than 1.75 mL/kg/hr was associated with significantly greater mortality (adjusted odds ratio, 1.15; 95% CI, 1.03–1.29; $p = 0.011$). Adjusted univariable mediation analysis found no suggestion of a causal mediation pathway for this effect by blood pressure, vasopressor therapy, or potassium levels, but identified a possible mediation effect for fluid balance (average causal mediation effect, 0.95; 95% CI, 0.89–1.00; $p = 0.060$) and percentage of phosphate measurements with hypophosphatemia (average causal mediation effect, 0.96; 95% CI, 0.92–1.00; $p = 0.055$). However, on multiple mediator analyses, these two variables showed no significant effect. In contrast, a high net ultrafiltration rate had an average direct effect of 1.24 (95% CI, 1.11–1.40; $p < 0.001$).

Conclusions: An early net ultrafiltration greater than 1.75 mL/kg/hr was independently associated with increased hospital mortality. Its putative effect on mortality was direct and not mediated by a causal pathway that included fluid balance, low blood pressure, vasopressor use, hypokalemia, or hypophosphatemia. (*Crit Care Med* 2020; 48:e934–e942)

Key Words: continuous renal replacement therapy; fluid balance; mediation analysis; mortality; net ultrafiltration

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Fluid balance (FB) management is a cornerstone of ICU management, especially in patients receiving continuous renal replacement therapy (CRRT) (1, 2). A higher hourly negative FB is usually achieved by increasing hourly net ultrafiltration (NUF) rate (3, 4). Several studies have reported that a negative FB is associated with decreased mortality (5–8). As a negative FB is typically achieved with greater NUF rates, greater NUF rate should also logically be associated with decreased mortality. Instead, a recent secondary analysis of the Randomized Evaluation of Normal versus Augmented Level

(RENAL) trial reported that a high NUF rate ($> 1.75 \text{ mL/kg/hr}$) was independently associated with increased mortality (9). Furthermore, more recently, using detailed hourly data from another large data set, a further independent study confirmed these findings (10).

Given the above observations, although high NUF rates might be associated with mortality, such association might be mediated by the FB achieved during CRRT. It is also possible that it might be mediated an indirect effect on other “mediators” such as hypotension, increased vasopressor use, hypokalemia, or hypophosphatemia, which may be directly affected by a high NUF and, then mediate its putative effect on mortality. Whether such mediation effect exists can be assessed with the statistical technique of multiple mediator analysis (11–13).

Accordingly, we studied a cohort of adult ICU patients treated with CRRT to assess whether the putative effect of NUF rate on mortality might not be direct, but, in fact, be mediated by its impact on three possible so-called mediation domains: FB, hemodynamic instability, and key electrolyte changes.

MATERIALS AND METHODS

Study Design

We performed a retrospective, observational study in a tertiary hospital affiliated to the University of Melbourne. This investigation was approved by the Austin Health Human Research Ethics Committee with a waiver of informed consent (Approval number: LNR/19/Austin/18).

Population

All critically ill patients admitted to the ICU during 2016–2018, who were treated with CRRT within 14 days of ICU admission, were considered. Patients who had received intermittent hemodialysis (IHD) and plasma exchange (PE) were excluded. In addition, to remove the competing effect of early mortality, patients who had died within 48 hours of ICU admission were also excluded.

Data Collection

We extracted and validated data from the ICU electronic database and scanned medical records. We focused data collection on CRRT hourly NUF rate and hourly FB as recorded in the electronic fluid chart during the early (first 48 hr) period of treatment. Hourly NUF rate was calculated as the difference between hourly fluid removal from the CRRT machine and hourly replacement fluid, infused pre- and/or post-filter in continuous venovenous hemofiltration or continuous venovenous hemodiafiltration mode. In current practice, early NUF rate is typically individualized according to baseline clinical characteristics and rate is then adjusted accordingly by the medical team in charge of patient care without body weight adjustment. We assessed FB as the final cumulative FB at the end of the first 48 hours. Full description is provided in **eAppendix 1** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

Exposure

The primary exposure was the NUF rate in the first 48 hours of CRRT, calculated from cumulative NUF volume in milliliters at the end of 48 hours divided by weight in kilograms at the beginning of CRRT and the duration of CRRT in hours. Full description is provided in **eAppendix 2** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

Study Outcome

Primary outcome was all-cause hospital mortality.

Statistical Analyses

According to a previous publication (9), we stratified NUF rate into three groups: 1) low ($< 1.01 \text{ mL/kg/hr}$); 2) middle ($1.01\text{--}1.75 \text{ mL/kg/hr}$); and 3) high ($> 1.75 \text{ mL/kg/hr}$). We reported categorical variables as numbers and percentages and compared them using the chi-square test. We reported continuous variables as median (quartile 25–75%) and compared the using the Wilcoxon rank-sum test.

To assess the association of NUF rate with mortality and its interaction with possible mediators, three domains likely to mediate the effect of a high NUF rate were assessed: 1) FB, 2) hemodynamic instability, and 3) status key electrolytes. The descriptions of the components assessed in each of these domains are described in **eAppendix 3** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

To visually assess the pathway of the relationship between NUF rate and mortality and its effect on FB, “alluvial” diagrams were also used. First, NUF rate was included according to the tertiles described above and then the FB according to quartiles from the cohort. Then, in a second approach NUF rate was included according to the same tertiles, but FB was included and stratified into three categories: 1) a positive FB ($> 2,000 \text{ mL}$); 2) a neutral FB ($-1,999$ to $2,000 \text{ mL}$); and 3) a negative FB ($< -2,000 \text{ mL}$).

For the hemodynamic domain, the NUF rate was included according to the same tertiles together with the presence or absence of hypotension during the first 48 hours.

For the electrolyte domain, NUF rate was included according to the same tertiles together with the presence or absence of hypokalemia or hypophosphatemia during the first 48 hours.

To investigate whether the difference in mortality among the different levels of NUF rate might be due to its impact on the mediators for each domain, a univariable and multivariable mediation model were used. Mediators are variables that are affected by group assignment and that subsequently can affect outcome. Therefore, mediators are on the causal pathway of the relation between group (in this case, NUF tertile) and outcome (in this case, mortality), at least potentially partly explaining the putative effects of the group on the outcome.

In the first step, we assessed the individual impact of each component of the domains described above as a potential mediator of the different mortality risk according to NUF rate in a univariable and then a multivariable model adjusted by Acute Physiology and Chronic Health Evaluation (APACHE) III, need for vasopressors at the start of CRRT, need of mechanical ventilation at the start of CRRT, and time from ICU admission

until start of CRRT. For this model, Quasi-Bayesian CIs were estimated after 10,000 simulations.

For the mediation models, the following estimates were described:

- 1) the total effect (estimate of the total putative effect of NUF rate on mortality);
- 2) the average causal mediation effect (ACME), a variable that explains how much of the putative effect of NUF rate on mortality is explained by the possible effect of the mediator; and
- 3) the average direct effect (ADE), a variable that explains how much of the putative effect of NUF rate on mortality is still explained by NUF rate after considering the effect of any given mediator.

A more detailed description of mediation analysis, as applied to this study, is described in **eAppendix 4** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

All effects are presented as odds ratio and with 95% CI.

For the final model, a univariable and multivariable (adjusted by the same covariates described above) multiple mediation model was conducted, including the most significant component of each domain together as potential mediators.

In this second model, the CIs were estimated by bootstrapping with 1,000 samples. All models compared high versus low tertiles and high versus middle tertiles.

Finally, in a sensitivity analysis, the cohort was stratified into two groups according to the higher cutoff of NUF rate (> 1.75 mL/kg/hr vs ≤ 1.75 mL/kg/hr). Furthermore, we conducted mediation analysis nested in time intervals of 6 hours for the FB domain. Additionally, we conducted a time-dependent Cox proportional hazard model (14) and joint model considering the hourly NUF rate as a continuous time-varying covariate.

A two-sided p value of less than 0.05 was considered as evidence of statistical significance. All analyses, including causal mediation analysis (15), were performed using R software, Version 3.6.0 (R Core Team, Vienna, Austria).

RESULTS

Study Population

Between July 30, 2016, and December 31, 2018, 4,774 critically ill patients were admitted to the study ICU and 423 were treated with CRRT and were, therefore, potentially eligible for the study. In total, 53 patients were then excluded due to the pre-CRRT use of IHD, PE, or because they had initiated CRRT later than 14 days. In addition, 19 patients who had died within 48 hours of ICU admission and six patients who had started CRRT greater than 14 days after ICU admission were excluded leaving 347 patients for analysis (**Fig. 1**).

Baseline characteristics of the study patients separated according to their NUF rate category are shown in **Table 1** (more extensive baseline characteristics are shown in **Table S1** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>) and their clinical outcomes are shown in **Table S2** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). The relationship

of NUF rate with FB, hemodynamic, electrolyte indices, and lactate levels is shown in **Table 2**. Furthermore, changes in lactate over time are shown in **Figure S1** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). For all domains and in the first 48 hours, cumulative FB was more negative, potassium and phosphate were lower, and the number of episodes of hypophosphatemia was greater in patients in the high NUF rate group.

Alluvial Diagrams

Alluvial plots demonstrated that the majority of deaths (represented by the gray alluvia) were seen by the combination of a NUF rate greater than 1.75 mL/kg/hr and a FB more negative than $-1,876$ mL or from the combination of a NUF rate less than 1.01 mL/kg/hr and a FB more positive than $+1,368$ mL (**Fig. S2A**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

Furthermore, in a second approach, the combined display of NUF rate and three categories of FB showed that the majority of deaths were seen by the combination of a NUF rate greater than 1.75 mL/kg/hr and a FB more negative than $-2,000$ mL, or the combination of a NUF rate less than 1.01 mL/kg/hr and a FB higher than $+2,000$ mL (**Fig. S2B**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

In the hemodynamic (**Fig. S3A**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>) and electrolyte (**Fig. S3, B and C**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>) domains, no clear pathway was found

Figure 1. Flow chart of inclusion. NUF = net ultrafiltration, RRT = renal replacement therapy.

TABLE 1. Baseline Characteristics According to Net Ultrafiltration Rate at ICU Admission and Before Continuous Renal Replacement Therapy

Characteristic	Net Ultrafiltration Rate Category			p
	< 1.01 mL/kg/hr (n = 159)	1.01–1.75 mL/kg/hr (n = 102)	> 1.75 mL/kg/hr (n = 86)	
Age, yr	64.0 (54.5–71.0)	65.0 (54.2–71.7)	61.5 (50.2–70.7)	0.302
Male gender	117 (73.6)	65 (63.7)	35 (40.7)	< 0.001
Weight, kg	86.0 (72.0–100.0)	86.5 (75.0–100.0)	70.5 (63.3–88.7)	< 0.001
Body mass index, kg/m ²	29.0 (24.6–33.9)	29.5 (26.3–35.3)	27.3 (23.8–32.2)	0.114
Acute Physiology and Chronic Health Evaluation III score	71.0 (53.5–87.0)	80.0 (53.0–93.7)	71.0 (56.2–89.5)	0.250
Pre-admission renal function				
Creatinine, μmol/L	119.0 (82.0–194.0)	114.5 (77.5–180.0)	92.5 (68.2–129.5)	0.006
Estimated glomerular filtration rate, mL/min/1.73 m ²	53.0 (25.5–79.0)	55.0 (31.0–86.2)	60.5 (45.0–90.7)	0.140
Comorbidities				
Hypertension	82 (51.6)	48 (47.1)	35 (40.7)	0.264
Diabetes mellitus	58 (36.5)	37 (36.3)	29 (33.7)	0.903
Coronary artery disease	47 (29.6)	35 (34.3)	22 (25.6)	0.423
Atrial fibrillation	24 (15.1)	16 (15.7)	5 (5.8)	0.074
End-stage renal disease	15 (9.4)	8 (7.8)	7 (8.1)	0.889
Chronic liver disease	25 (15.7)	20 (19.6)	18 (20.9)	0.542
Cancer	26 (16.4)	19 (18.6)	17 (19.8)	0.779
Immunosuppression	33 (20.8)	20 (19.6)	22 (25.6)	0.574
ICU admission diagnosis				
Nonsurgical admission				0.004
Cardiovascular	21 (19.3)	18 (25.4)	11 (15.9)	
Genitourinary	29 (26.6)	11 (15.5)	6 (8.7)	
Respiratory	11 (10.1)	13 (18.3)	15 (21.7)	
Gastrointestinal	31 (28.4)	21 (29.6)	33 (47.8)	
Other	17 (15.6)	8 (11.3)	4 (5.8)	
Surgical admission				0.253
Cardiovascular	31 (62.0)	15 (48.4)	6 (35.3)	
Gastrointestinal	14 (28.0)	13 (41.9)	7 (41.2)	
Other	5 (10.0)	3 (9.7)	4 (23.5)	
Before CRRT initiation				
Mechanical ventilation	100 (62.9)	70 (68.6)	63 (73.3)	0.239
Need for vasopressor	109 (68.6)	61 (59.8)	47 (54.7)	0.079
Sepsis or septic shock	43 (27.0)	23 (22.5)	30 (34.9)	0.165
Cardiac arrest	6 (3.8)	13 (12.7)	8 (9.3)	0.025
Fluid overload	10 (6.3)	12 (11.8)	12 (14.0)	0.114
Oliguria	99 (62.3)	67 (65.7)	48 (55.8)	0.374
Laboratory before CRRT				
Creatinine, μmol/L	350.0 (204.5–501.5)	319.0 (231.5–433.7)	250.5 (162.7–335.0)	0.001
Urea, mmol/L	21.0 (13.2–28.4)	21.0 (12.9–29.9)	17.6 (9.6–28.2)	0.203
pH	7.35 (7.27–7.39)	7.35 (7.27–7.41)	7.33 (7.25–7.39)	0.743
Potassium, mmol/L	4.5 (4.0–5.2)	4.5 (3.9–5.2)	4.3 (3.9–4.8)	0.108
Bicarbonate, mmol/L	19.0 (15.7–23.0)	20.0 (17.0–23.9)	19.0 (16.0–23.0)	0.211
Base excess, mmol/L	−5.0 (−10.0 to −2.0)	−4.0 (−8.0 to −0.8)	−5.2 (−9.0 to −1.9)	0.225
Lactate, mmol/L	2.1 (1.2–4.2)	1.9 (1.4–3.4)	2.0 (1.3–4.6)	0.805
PaO ₂ /Fio ₂	287.9 (210.9–381.5)	275.0 (200.0–352.7)	282.5 (222.5–420.0)	0.469
Mean arterial pressure, mm Hg	74.0 (67.5–80.0)	75.0 (70.0–86.0)	75.5 (67.0–85.0)	0.268
Urine output 6 hr, mL/kg/hr	0.29 (0.05–0.86)	0.18 (0.05–0.53)	0.48 (0.14–0.94)	< 0.001
Time to start CRRT from ICU admission, hr	9.0 (3.1–33.2)	13.4 (3.1–40.9)	19.0 (3.8–47.5)	0.293

CRRT = continuous renal replacement therapy. Data are median (quartile 25–75%) or n (%).

TABLE 2. Fluid Balance, Hemodynamic Indices, and Electrolytes Stratified by Net Ultrafiltration Rate Group Within 48 Hours of Continuous Renal Replacement Therapy Treatment

Indices	< 1.01 mL/kg/hr (n = 159)	1.01–1.75 mL/kg/hr (n = 102)	> 1.75 mL/kg/hr (n = 86)	p
Fluid balance, mL				
Before continuous renal replacement therapy	215 (–272 to 1,189)	310 (–32 to 2,095)	682 (–28 to 2,908)	0.038
Day 1	533.0 (–304.5 to 1,647.0)	–4.0 (–909.7 to 780.0)	–149.5 (–1,249.0 to 627.0)	< 0.001
Day 2	118.0 (–876.2 to 984.0)	–940.0 (–1,710.5 to 15.2)	–1,364.0 (–2,244.0 to –321.0)	< 0.001
Cumulative	527.0 (–824.0 to 2,400.0)	–657.0 (–2,171.7 to 600.0)	–1,751.0 (–3,477.7 to 376.0)	< 0.001
Coefficient of variation of net ultrafiltration rate, %	102.5 (73.3–165.6)	67.1 (51.5–80.5)	48.8 (40.6–66.2)	< 0.001
Hemodynamic				
Hypotension ^a	93 (58.5)	56 (54.9)	44 (51.2)	0.537
Time-weighted average MAP, mm Hg	73 (67–81)	73 (69–81)	76 (69–82)	0.190
Lowest MAP in the first 48 hr	62 (59–67)	63 (60–68)	63 (60–68)	0.474
Coefficient of variation of MAP, %	9.0 (7.2–11.8)	9.4 (7.7–11.0)	9.1 (7.8–10.9)	0.830
^b Amplitude of MAP, mm Hg	15.0 (10.6–19.9)	16.2 (11.1–20.1)	16.2 (11.9–20.4)	0.289
Number of episodes of hypotension ^a	1 (0–4)	1 (0–2)	1 (0–3)	0.374
% of measurements with hypotension	3.4 (0.0–12.3)	2.5 (0.0–6.9)	2.1 (0.0–8.0)	0.231
Need of vasopressor	122 (76.7)	72 (70.6)	57 (66.3)	0.195
Hours with vasopressors	22 (2–29)	21 (0–32)	12 (0–32)	0.731
Total dose norepinephrine-equivalent	109.0 (2.7–371.5)	77.0 (0.0–294.3)	42.0 (0.0–235.5)	0.139
Norepinephrine total dose	109.0 (2.7–357.0)	75.5 (0.0–291.0)	42.0 (0.0–235.5)	0.148
Epinephrine total dose	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.064
Vasopressin total dose	0.00 (0.00–0.08)	0.00 (0.00–0.04)	0.00 (0.00–0.00)	0.279
Phenylephrine total dose	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.207
Lowest central venous pressure, mm Hg	8 (5–10)	8 (5–11)	7 (5–10)	0.671
Coefficient of variation of central venous pressure, %	20.2 (14.2–26.7)	19.9 (14.6–28.0)	20.9 (16.0–28.4)	0.607
Electrolytes and acid-base				
Hypokalemia ^c	29 (18.2)	19 (18.6)	23 (26.7)	0.249
Lowest potassium, mmol/L	3.80 (3.55–4.10)	3.80 (3.60–4.00)	3.70 (3.40–3.90)	0.030
Number of episodes of hypokalemia	0 (0–0)	0 (0–0)	0 (0–1)	0.203
% of measurements with hypokalemia	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–6.8)	0.274
Hypophosphatemia ^d	22 (14.4)	13 (12.9)	23 (27.1)	0.018
Lowest phosphate, mmol/L	1.37 (1.04–1.73)	1.34 (1.07–1.67)	1.19 (0.75–1.50)	0.006
Number of episodes of hypophosphatemia	0 (0–0)	0 (0–0)	0 (0–1)	0.011
% of measurements with hypophosphatemia	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–16.7)	0.022
Lowest pH	7.32 (7.25–7.38)	7.33 (7.26–7.38)	7.31 (7.25–7.38)	0.706
Mean daily lactate, mmol/L	2.07 (1.52–3.57)	1.91 (1.48–2.86)	2.29 (1.63–4.10)	< 0.001
Highest lactate, mmol/L	3.40 (2.10–5.75)	2.75 (2.10–4.37)	3.25 (2.22–5.87)	< 0.001

MAP = mean arterial blood pressure.

^aMAP < 65 mm Hg.^bDifference between the maximum MAP and the mean MAP in the period of 48 hr.^cPotassium < 3.5 mmol/L.^dPhosphate < 0.81 mmol/L. Coefficient of variation defined as the sd of the hourly net ultrafiltration rate divided by its mean and multiplied by 100. Vasopressors defined as any need of norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine. Data are median (interquartile range) or n (%).

between NUF rate, hypotension, hypokalemia, hypophosphatemia, and mortality.

Mediation Analyses

In unadjusted mediation analysis, the putative impact of a high NUF rate on mortality appeared partially mediated by its effect on FB (unadjusted ACME, 0.91; 95% CI, 0.85–0.97; $p = 0.002$) with an additional and significant direct putative effect of high NUF on mortality (unadjusted ADE, 1.22; 95% CI, 1.09–1.39; $p = 0.001$) (Table S3, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

After adjustment for confounders (APACHE III, need for vasopressors at start of CRRT, need of mechanical ventilation at start of CRRT, and time from ICU admission until start of CRRT) and on single mediator analysis, however, the mediation effect of FB was no longer significant (adjusted ACME, 0.95; 95% CI, 0.89–1.00; $p = 0.060$). In contrast, the direct effect of high NUF rate was still present after such adjustments (adjusted ADE, 1.20; 95% CI, 1.06–1.35; $p = 0.003$) (Table S3, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

No variable assessed in the hemodynamic domain significantly mediated the putative effect of high NUF rate on mortality (Table S4, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). However, after adjustments and in all analyses with different mediators, the significant direct effect of high NUF rate persisted.

On unadjusted analysis, the putative effect of high NUF rate on mortality appeared partially mediated by its effect on phosphate, assessed as the percentage of phosphate measurements in the hypophosphatemic range in the first 48 hours (unadjusted ACME, 0.96; 95% CI, 0.92–1.00; $p = 0.032$). However, after adjustment for confounders, on single mediator analysis, this mediation effect was no longer significant (Table S5, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). As in other analyses, a significant direct effect of high NUF rate remained.

In a multiple mediator analysis model, taking into account the positive mediators described above with single mediator analysis (FB and the number of percentage of measurement with hypophosphatemia in the first 48 hr), and after adjustment for confounders (APACHE III, need for vasopressors at start of CRRT, need of mechanical ventilation at start of CRRT, and time from ICU admission until start of CRRT) no mediator explained the putative effect of high NUF rate on mortality (Table 3). However, the significant direct effect of high NUF rate remained (adjusted ADE, 1.24; 95% CI, 1.11–1.40; $p < 0.001$).

Sensitivity Analysis

When stratifying the cohort into two groups according to the higher cutoff of NUF rate (> 1.75 vs ≤ 1.75 mL/kg/hr), after adjustment for confounders, there was also a significant association between higher NUF rate and mortality but, on single mediation analysis, this putative effect was not mediated by any possible mediation domains (Tables S3–S5, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). The

same was found on multiple mediation analyses (Table 3). Furthermore, the result of mediation analysis nested in time intervals of 6 hours for the FB domain was stable according to the cutoffs of NUF rate (Table S6 and Fig. S4, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>). In addition, the time-dependent Cox proportional hazard model including NUF as time-varying covariate showed no significant variation in NUF rate over the study period (adjusted hazard ratio, 0.98; 95% CI, 0.80–1.19; $p = 0.843$) and no interaction between FB and NUF rate ($p = 0.219$). (Table S7, Supplemental Digital Content 1, <http://links.lww.com/CCM/F693>).

DISCUSSION

Key Findings

In a cohort of CRRT-treated patients, we investigated whether the association between early NUF rate and mortality is mediated not by a direct effect, but rather by its impact on FB, or hypotension, or use of vasopressors, or hypokalemia or hypophosphatemia. We found that, in the first 48 hours, a low NUF rate with a positive FB or a high NUF rate with a marked negative FB was particularly associated with increased mortality. However, on single and multilevel mediation analysis, none of the hypothesized mediators showed a significant mediating impact on mortality. In contrast, an early NUF greater than 1.75 mL/kg/hr continued to have a direct effect on mortality compared to a NUF less than 1.01 mL/kg/hr.

Relationship With Previous Studies

FB management in CRRT-treated patients is achieved primarily via adjustments in the NUF rate. Although a negative FB is consistently associated with favorable outcomes, no studies of CRRT cohorts have described the relationship between FB and NUF rate (16–18). A substudy of the RENAL trial (i.e., a trial of intensity of CRRT in the critically ill with AKI), demonstrated an association between negative mean daily FB and decreased risk of death (6). However, recently, Murugan et al (9) reported a further analysis of the RENAL study cohort and found that a NUF rate greater than 1.75 mL/kg/hr was independently associated with increased mortality. These findings were more recently confirmed even for the possible effect of early (first 48 hr) NUF in a large cohort of CRRT-treated patients (10). Despite these findings and the potential harm associated with high NUF rates, a multinational survey on NUF prescription reported that the acceptable maximum NUF prescribed for hemodynamically stable patients was more than 200 mL/hr (> 2 mL/kg/hr in a 80 kg patient) (19). Finally, a recent retrospective study also demonstrated that a NUF rate higher than 25 mL/kg/d (approximately 1 mL/kg/hr and mimicking the middle tertile of NUF rate of our study) was associated with a decreased 1-year risk-adjusted mortality (20).

The findings that higher NUF rates may contribute to a higher mortality risk are also consistent with a previous observational study in chronic hemodialysis patients, showing that a high NUF rate was associated with increased cardiovascular mortality (21, 22) Possible mechanisms to explain

TABLE 3. Multiple Mediation Analyses for Hospital Mortality As Outcome and According to the Higher and Lower Tertile of Net Ultrafiltration Rate and With Fluid Balance and Percentage of Hypophosphatemia As Mediators^a

Exposure Variable	Unadjusted OR (95% CI) ^b	<i>p</i>	Adjusted OR (95% CI) ^{a,b}	<i>p</i>
Exposure: NUF rate (> 1.75 vs < 1.01 mL/kg/hr)				
Fluid balance (continuous) as mediator				
Total effect of higher NUF rate	1.15 (1.01–1.29)	0.025	1.15 (1.03–1.29)	0.011
ACME of fluid balance	0.92 (0.86–0.97)	0.008	0.95 (0.90–0.99)	0.062
ACME of percentage of hypophosphatemia	0.97 (0.94–1.00)	0.101	0.98 (0.94–1.01)	0.136
ADE of higher NUF rate	1.28 (1.13–1.47)	< 0.001	1.24 (1.11–1.40)	< 0.001
Exposure: NUF rate (> 1.75 vs 1.01–1.75 mL/kg/hr)				
Fluid balance (continuous) as mediator				
Total effect of higher NUF rate	1.07 (0.94–1.23)	0.309	1.11 (0.97–1.26)	0.114
ACME of fluid balance	0.99 (0.97–1.02)	0.711	0.99 (0.97–1.03)	0.959
ACME of percentage of hypophosphatemia	0.99 (0.94–1.00)	0.377	0.99 (0.95–1.01)	0.558
ADE of higher NUF rate	1.09 (0.95–1.26)	0.213	1.12 (0.98–1.27)	0.095
Exposure: NUF rate (> 1.75 vs ≤ 1.75 mL/kg/hr)				
Fluid balance (continuous) as mediator				
Total effect of higher NUF rate	1.12 (0.99–1.25)	0.057	1.14 (1.02–1.27)	0.019
ACME of fluid balance	0.96 (0.92–0.99)	0.041	0.98 (0.95–1.02)	0.281
ACME of percentage of hypophosphatemia	0.98 (0.95–1.00)	0.144	0.98 (0.96–1.00)	0.250
ADE of higher NUF rate	1.18 (1.05–1.33)	0.006	1.17 (1.05–1.32)	0.005

ACME = average causal mediation effect, ADE = average direct effect, NUF = net ultrafiltration, OR = odds ratio.

^aAdjusted by Acute Physiology and Chronic Health Evaluation III, need of mechanical ventilation, and need for vasopressor and time until renal replacement start.

^bAll estimates and Quasi-Bayesian CIs generated after 10,000 simulations. Phosphate and fluid balance selected as variables because of suggestion of mediation in single variable mediation analysis.

the relationship between a greater NUF and mortality include myocardial stunning, hemodynamic instability, electrolyte imbalances, increased circulating endotoxemia and bacterial translocation, and decreased therapeutic drug level (23–34). In our study cohort, however, the effect of NUF on increased mortality in the first 48 hours of CRRT did not appear mediated by its effect on FB, hemodynamic instability, or electrolyte disturbances.

Implication of Study Finding

Our findings imply that, in the first 48 hours, NUF is a modifiable risk factor for mortality in patients receiving CRRT, and a NUF rate below and above the optimal middle rate may be harmful. Furthermore, they imply that this relationship is not significantly mediated by its impact on FB or hemodynamic instability or potassium or phosphate disturbances and may instead be mediated by other events (e.g., subcardiovascular stress not detected by blood pressure change [23]). Thus, our findings imply that other confounders or not yet identified factors in our study may mechanistically mediate the putative effect of a high early NUF on mortality. Future studies should

focus on changes in the microcirculation in response to high NUF rates.

Study Strengths and Limitations

To our knowledge, this is the first study to assess the mediation-affected relationship between early NUF rate, FB, vasopressor therapy, and electrolyte disturbances and mortality. Furthermore, this is a large cohort of CRRT-treated patients from a tertiary hospital in a developed country that was also one of the study sites in the RENAL trial, making the findings relevant to similar ICUs in resource-rich countries. In addition, it was based on highly granular hourly NUF rate data. Finally, we removed the competing risk of death by excluding patients who did not survive in the first 48 hours, thus eliminating this risk of bias.

We acknowledge limitations to this study. First, this is a single center, retrospective observational study, with the shortcomings inherent to such studies and had limitations in number of patients in each group. However, our patients had baseline characteristics similar to those from larger studies. Second, hemodynamic data were recorded hourly. Accordingly, it is possible that transient hemodynamic instability episodes

might not have been recorded, thus creating a degree of ascertainment bias or microcirculation dysfunction despite stable systemic hemodynamics. However, to our knowledge, this is the first study to report hourly hemodynamic data during CRRT and will likely open the door to further continuous measurements of changes in hemodynamics and FB (e.g., Pulse Contour Continuous Cardiac Output, bioelectrical impedance vector analysis) (35, 36) during CRRT and assessment of the microcirculation (e.g., lactate, delta P_{CO_2} gap, microcirculation microscopy) in response to a high NUF rate. Similarly, we only measured phosphate levels daily and potassium levels every 4 to 6 hours, creating a similar ascertainment bias for such electrolyte disturbances. Third, although we adjusted for potential confounding, the relationship between NUF rate and mortality may still be mediated and influenced by other unmeasured confounders, and this could bias the estimate of indirect and direct effects.

CONCLUSIONS

In the first 48 hours, among patients in a large CRRT-treated cohort, a NUF greater than 1.75 mL/kg/hr was independently associated with increased hospital mortality. This association was not mediated by the impact of such NUF rate on FB or hemodynamic instability or electrolyte disturbances. Further investigations are required to identify mechanistic factors that might mediate the putative effect of high NUF on mortality among CRRT-treated patients.

Drs. Naorunroj, Eastwood, and Bellomo involved in research ideas and study design. Drs. Naorunroj, Neto, and Zwakman-Hessels involved in data acquisition. Dr. Neto involved in statistical analysis. Drs. Neto, Murugan, Kellum, and Bellomo involved in supervision or mentorship. All authors involved in data analysis/interpretation. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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